REMARKS

Interview

Applicants thank Examiner Le for his willingness to make himself available at the last minute for the February 8, 2005 personal interview and his consideration of applicants' arguments.

As noted in the Interview Summary Record and discussed in more detail below, various stated differences between applicants' method and the prior art of record were discussed.

Status of the Claims

The amendments and remarks presented herein place the claims in condition for allowance. Applicants respectfully request reconsideration in view of these amendments and arguments.

Prior to this amendment, claims 6, 7, and 9-14 were pending and had been examined.

Applicants have amended claims 6 and 9-14. Applicants have also canceled claim 7 and incorporated its substance into the remaining claims. Applicants have also added claims 27 and 28.

Claims 6, 9-14, 27, and 28, thus, are now pending in this application.

Amendments to the Claims

Claim 6

Applicants have amended claim 6 to more particularly point out and distinctly claim their invention. None of these amendments introduces new matter. They are fully supported by the specification and claims as originally filed. Applicants request their entry.

In particular, applicants have amended claim 6 to make clear that the correlation recited in step (g) is a correlation between the predicted masses of the candidate proteins and the masses determined for the differentially displayed proteins. Support for this amendment can be found in applicants' specification, for example, at page 109, line 22 to page 110, line 6. This amendment does not narrow the scope of the original claims. It merely clarifies the data that is correlated in this step of the claimed method.

Claims 27 and 28

Applicants have added claims 27 and 28 (both depend from claim 6) to more particularly point out and distinctly claim their invention. The addition of these claims does not introduce new matter. They are fully supported by the specification and claims as originally filed. Applicants request their entry.

In claim 27, the differentially displayed protein cleavage product is characterized by determining a portion of

its amino acid sequence by tandem mass spectrometry. Candidate proteins that include this amino acid sequence are then identified. Support for this claim can be found in applicants' specification, for example, at page 73, line 18 to page 74, line 2.

In claim 28, at least one tandem mass spectrum of at least one of the differentially displayed protein cleavage products is determined. Candidate proteins whose predicted tandem mass spectra correspond to the tandem mass spectra of the cleavage product are then identified. Support for this claim can be found in applicants' specification, for example, at page 73, lines 4-17.

Claims 7 and 9-14

Applicants have also amended claims 9-14 to correspond them to amended claim 6. None of these amendments introduces new matter. They are fully supported by the specification and claims as originally filed. Applicants request their entry.

Finally, applicants have canceled claim 7 and incorporated its substance into the remaining claims.

Rejections Under 35 U.S.C. § 103

Hutchens and Dongre

Claims 6 and 9-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hutchens et al., PCT

international publication WO 98/59362 ("Hutchens") in view of Dongre et al., "Emerging Tandem Mass-Spectrometry Techniques for the Rapid Identification of Proteins," TIBTECH, Vol. 15, pp. 418-428, October 1997 ("Dongre"). Claim 7 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Hutchens in view of Dongre and in further view of Little et al., U.S. Patent 6,322,970 ("Little"). Applicants traverse these rejections. They have amended claim 6 to better clarify the patentable differences between their method and the cited documents.

Applicants' claimed invention is directed to a method for identifying at least one protein that is differentially displayed in the mass spectra of two complex biological samples. The method combines two different approaches to protein detection in order to identify a protein whose presence, concentration, or characteristics differs between the two samples.

In the first approach, set forth in claim 6, steps (a) and (b), the two samples are subjected to mass spectrometry to determine the mass of at least one differentially displayed protein. In the second approach, set forth in claim 6, steps (c)-(f), cleavage products from the two samples are subjected to mass spectrometry to detect at least one differentially displayed protein cleavage product (steps (c) and (d)). The differentially displayed protein cleavage product is then characterized by tandem mass spectrometry (step (e)). This step produces information (e.g., amino acid sequence information or other characteristics) that is used to identify a candidate protein from which the differentially displayed

protein cleavage product may have been derived, and the predicted mass of that candidate protein is determined (step (f)).

At this point, the information from the two approaches is merged. Indeed, step (g) recites correlating the predicted mass of the candidate protein from step (f) with the measured mass of the differentially displayed protein from step (b). The claimed process, therefore, allows one to integrate protein cleavage fragment information derived from tandem mass spectrometry with information about a protein detected directly in a sample. As discussed during the interview, none of the cited documents, alone or in combination, discloses or suggests such combination of these two approaches for the identification of a protein that is differentially displayed between two samples.

The Examiner argues that Hutchens taught differential expression of analytes using desorption spectrometry and also taught fragmenting proteins into smaller pieces in order to increase sensitivity. However, Hutchens did not disclose any method of correlating information obtained from the differential presence of a protein in an analyte with information obtained from fragmenting that protein in order to identify the differentially displayed protein.

The Examiner argues further that Dongre taught methods of identifying proteins using tandem mass spectrometry and that it would have been obvious for one of ordinary skill in the art to modify Hutchens to include the tandem mass spectrometry and secondary fragmentation as taught by Dongre.

However, there was no suggestion to combine the Hutchens and Dongre approaches and even if there were, the combination still would fall far short of including the correlation step (g) of claim 6.

Dongre disclosed the analysis of polypeptides by tandem mass spectrometry. In one method (Dongre at page 423, Figure 4), proteins are separated by gel electrophoresis, the spots are subject to proteolytic digestion, and the fragments are subjected to LC-MS-MS. However, Dongre did not suggest performing MS-MS on fragments of proteins shown to be differentially present in a sample by prior mass spectrometry. Therefore, there was no suggestion in Dongre to combine those methods.

However, even if there were suggestion to combine those methods, the "combination" would have still lacked correlation step (g) of claim 6. Dongre referred to an analysis of the peptides detected by tandem MS by searching a protein database to obtain a list of peptides with matching masses and their respective protein sources. (See Dongre at page 421, right column, last paragraph.) However, there was no teaching to determine the predicted masses of those "protein sources" or to correlate those predicted masses with the mass of a differentially expressed protein that was detected in the samples before protein cleavage. Because there was no suggestion to combine the teachings of Dongre and Hutchens, and because even when combined, the combination lacked a step (step (g)) of the claimed method, that combination did not render the claimed invention obvious.

Therefore, Hutchens and Dongre, either alone or in combination, did not teach, suggest, or motivate the skilled worker to practice a method having all of the features of applicants' amended claim 6. Moreover, Hutchens and Dongre, either alone or in combination, did not teach, suggest, or motivate the skilled worker to practice a method having all of the features of claims 9-14, 27, and 28, which all depend from claim 6. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these rejections

Liebler and Dongre

Claims 6 and 9-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Liebler et al., U.S. Patent 6,379,970 ("Liebler") in view of Dongre. Applicants traverse these rejections. They have amended claim 6 to better clarify the features that make their method patentably different from the cited documents.

As described above, applicants' claimed invention is directed to a method for identifying at least one protein that is differentially displayed in the mass spectra of two complex biological samples. To carry out this method of identification, amended claim 6 requires that two protein masses be determined and compared for each differentially displayed protein. These two protein masses are determined by two different approaches. One is determined by mass spectrometry. The other is predicted from a candidate protein that is identified based on tandem mass spectrometry

characterization of a protein cleavage product. The differentially displayed proteins can be identified by correlating the two masses.

Liebler and Dongre, either alone or in combination, did not teach, suggest, or motivate the skilled worker to practice a method having all of the features of applicants' claimed invention. In particular, these documents did not disclose that differentially displayed proteins can be identified by correlating two protein masses.

Amended claim 6 clarifies that applicants' method includes the steps of (a) adsorbing separately a subset of proteins from two biological samples to a probe surface, and (b) determining the mass of at least one differentially displayed protein by LDI mass spectrometry. As described above, the masses determined in step (b) constitute the first protein mass necessary for the correlation step (g).

Having determined the mass of at least one differentially displayed protein, at least a portion of the adsorbed proteins is cleaved. Following cleavage, the differentially displayed protein cleavage products are characterized by tandem mass spectrometry and those characteristics are used to identify possible candidate proteins. The predicted mass of at least one of the candidates constitute the second mass. Thus, the two masses are derived from two different sources: the first is derived from the adsorbed, uncleaved proteins, while the second is predicted from candidate proteins that include the characteristics of the protein cleavage products. Correlation, which is necessary for

identification of the differentially displayed protein, thus, requires both masses.

In contrast, Liebler did not teach or suggest steps (a) or (b) of applicants' amended claim 6, and hence did not determine the masses of differentially displayed proteins. Instead, Liebler made abundantly clear that its method begins with the "digesting of two samples," followed by "detection and selection of peptides that are present in different amounts in the two samples." (Liebler at column, 3, lines 41-44, emphasis added.) As a result, Liebler, either alone or in combination with Dongre, provided no teaching or suggestion that any masses of uncleaved proteins are ever determined by LDI mass spectrometry.

Instead, Liebler only disclosed the characterization of digested peptides. Having characterized these peptides, Liebler presumed that the presence of a peptide in the sample indicates the presence of the parent protein, stating that the "sequence identification of one or more such peptides in a protein digest is sufficient to establish the presence of the precursor protein in a sample with a high degree of confidence." (Liebler at column 3, lines 24-28, emphasis added.) Liebler contains no teaching or suggestion that the mass of any differentially displayed "precursor protein," prior to digestion, is ever determined by LDI mass spectrometry. Thus, Liebler's method never conclusively identifies the differentially displayed protein.

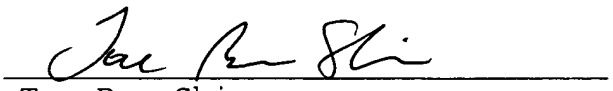
Therefore, Liebler and Dongre, either alone or in combination, did not teach, suggest, or motivate the skilled

worker to practice a method having all of the features of applicants' amended claim 6. Moreover, Liebler and Dongre, either alone or in combination, also did not teach, suggest, or motivate the skilled worker to practice a method having all of the features of claims 9-14, 27, and 28, which all depend from claim 6. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these rejections.

CONCLUSION

Applicants respectfully submit that all of the pending claims are in form for allowance. If the Examiner believes, however, that any matters remain outstanding, applicants respectfully request that the Examiner call the undersigned.

Respectfully submitted,



Tae Bum Shin
Limited recognition pursuant
to 37 C.F.R. §11.9(b)
Agent for Applicants

James F. Haley, Jr.
Reg. No. 27,794
Attorney for Applicants

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
Customer No. 1473
1251 Avenue of the Americas
New York, New York 10020-1105
Tel.: (650) 617-4000 (CA)
Fax: (212) 596-9090 (NY)